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Malignant pleural mesothelioma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Malignant pleural mesothelioma (MPM) is a rare tumor. The incidence is 1.25/100 000 in Great Britain and 1.1/100 000 in Germany. Within the next 20 years the incidence is estimated to double in many countries. Exposure to asbestos is a well-established etiological factor for MPM, with occupational exposure having been documented in 70%–80% of those affected.

diagnosis

Patients typically present with shortness of breath due to pleural effusion or chest pain in a more advanced stage. The diagnosis is usually suggested by imaging studies (unilateral pleural thickening; pleural effusion). An occupational history must be obtained.

Cytological examination of the effusion can be diagnostic, but often shows equivocal results. Therefore, histology, including immunohistochemistry, is the gold standard. Video-assisted thoracoscopy or open pleural biopsy in a fused pleural space may be necessary to provide sufficient material for accurate histological diagnosis. There are three main histological types (epithelial, sarcomatous and mixed), with ~60% being epithelial.

Recent data suggest the possible contribution of serum mesothelin-related proteins and osteopontin as useful markers to support the diagnosis of mesothelioma; however, the precise role of these markers is yet to be defined.

staging and risk assessment

Clinical staging is based on a thoracic CT scan; however, the translation of the images into TNM (tumor–node–metastasis) stages is often not conclusive. Mediastinoscopy and video-assisted thoracoscopy may be useful in determining the stage. Accurate initial staging is essential to provide both prognostic information and guidance on the most appropriate therapeutic options. Several different staging systems exist; among them is the international staging system for MPM, which emphasizes the extent of disease after surgery in a traditional TNM system and stratifies patients into similar prognostic categories (Table 1).

The Cancer and Leukemia Group B and the European Organization for Research and Treatment of Cancer prognostic scores may be used. They include performance status, age, histological type, weight loss and white blood count.

MPM rarely metastasizes to distant sites but most patients present with locally advanced disease. The use of PET scan to rule out extra-thoracic metastasis is under investigation and findings seem promising.

treatment

surgery

Different surgical procedures have been tested with varying degrees of success.

Extra-pleural pneumonectomy (EPP) with resection of the hemidiaphragm and the pericardium *en bloc* has the potential for a radical treatment and this approach is generally combined with neoadjuvant chemotherapy and/or adjuvant radiotherapy. Surgery, the appropriateness of which is still under consideration, should only be performed on selected patients by experienced thoracic surgeons in the context of a multidisciplinary team and preferably as part of a clinical trial [III, A]. Selection criteria include good performance status, earlier stage disease with not more than localized involvement of the thoracic wall and adequate cardiopulmonary function. The inclusion of patients with N2 or sarcomatoid disease is controversial. Pleurectomy/decortication may be indicated for elderly patients, at early stages or when EPP would leave macroscopic tumor behind.

To optimally palliate patients from dyspnea and pain, local procedures to control pleural effusion includes parietal pleurectomy or talc pleurodesis.

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Table 1. International staging system for malignant pleural mesothelioma

Stage	TNM	Comments
Ia	T1a N0 M0	Primary tumor limited to ipsilateral parietal pleura
Ib	T1b N0 M0	As stage Ia plus focal involvement of visceral pleura
II	T2 N0 M0	As stage Ia or Ib plus confluent involvement of diaphragm or visceral pleura or involvement of the lung
III	Any T3 M0, any N1 M0, any N2 M0	Locally advanced tumor; ipsilateral, bronchopulmonary or hilar lymph node involvement; subcarinal or ipsilateral mediastinal lymph node involvement
IV	Any T4, any N3, any M1	Locally advanced technically unresectable tumor; contralateral mediastinal, internal mammary and ipsilateral or contralateral supraclavicular lymph node involvement; distant metastases

radiotherapy

The use of hemithoracic radiotherapy has been limited because of severe side effects of irradiation of the underlying lung. Conventional radiotherapy dose can be delivered locally as a palliative measure for pain management. Modern radiotherapy techniques allow for delivering high-dose radiotherapy in an attempt to improve local control after extrapleural pneumonectomy. Caution must be exercised regarding the exposure of the contralateral lung to low-dose irradiation. Mesothelioma invades the tracts made by chest instrumentation. However, prophylactic radiotherapy to reduce the incidence of port metastases is controversial and not routinely applied.

chemotherapy

Platinum analogues, doxorubicin and some antimetabolites (methotrexate, raltitrexed and pemetrexed) have shown modest single agent activity [III, B].

The combinations of both pemetrexed/cisplatin and raltitrexed/cisplatin have been shown to improve survival as well as lung function and symptom control in comparison with cisplatin alone in randomized trials [II, A]. The combination pemetrexed/carboplatin is an alternative effective therapy [III, A].

A phase III trial evaluated second-line pemetrexed versus best supportive care in patients not previously exposed to this agent and found a longer time to disease progression in the chemotherapy arm.

If extrapleural pneumonectomy is planned, platinum-based neoadjuvant or adjuvant combination chemotherapy should be considered.

response evaluation

Response evaluation using CT scan is recommended after two to three chemotherapy cycles and the modified RECIST criteria should be applied.

follow-up

Follow-up consists of clinical evaluation, with particular attention to symptoms or chest wall recurrence, and a thoracic CT scan as needed.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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